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Comparative Study of Regulatory Requirements for Post-Approval Changes in US, EUROPE & SOUTH AFRICA

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ABSTRACT:

Chemistry, Manufacturing and Controls (CMC) changes are inevitable due to many reasons including changing needs, new findings and continuous improvement. Therefore, regulations require that all changes be evaluated carefully and follow the proper regulatory path for implementation, regardless of whether it is an investigational or a commercial product. Failure to comply with regulatory requirements for post- approval CMC changes can potentially lead to “misbranded or adulterated” status for a given product. This should be taken very seriously for marketed products because of the potential safety/efficacy impact for the vast number of patients as well as legal, regulatory and business impact for the sponsor. In light of QbD paradigm, leveraging the product and process knowledge gained and the use of a risk based approach should allow a sponsor to achieve the best path for post-approval change implementation. So This guidance provides recommendations to sponsors of new drug applications (NDA's), abbreviated new drug applications (ANDA's), and abbreviated antibiotic applications (AADA's) who intend, during the postapproval period, to change in US, EU, SOUTH AFRICA.

Key words: USFDA, EMA, MCC, Post approval changes, Regulatory Authorities

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INTRODUCTION [1]

“PRODUCTS RARELY STAY THE SAME”

During their life cycle, medicinal products are generally having many changes. The product rarely stays the same in original condition. The driving forces for these changes are manifold, e.g., the need to introduce process and production improvements, market demands, the continuously evolving requirements of regulatory bodies. There are many reasons for making change to pharmaceutical products after the original regulatory approval is obtained. For each change, it is necessary to find out the acceptability of the proposed changes, in order to prove that the specified change does not have an adverse effect on the product. Some of these changes may be significant and require a substantial amount of stability data while others are minor and may only require a stability commitment. The type of change will dictate the amount of data needed and the type of regulatory reporting required. The company change control is used to determine detail how changes are evaluated and implemented and how the change impacts stability. The regulatory group determines the strategy which may be more complex if the product is marketed globally and this strategy made for submission based on review of the technical assessment of the change and the appropriate regulatory guidance.

"Once a product is commercialized, at some point in its life cycle, something will change”.

-A

REGULATORY REQUIREMENTS ON POST-APPROVAL CHANGES IN US, EUROPE & SOUTH AFRICA

TABLE 1: TYPES OF POST APPROVAL CHANGES

FDA[1,2]	EMA[3-6]	MCC[7]
Major Change • Substantial Potential to have an adverse effect on the identity, strength, quality, purity, or potency of a drug product. • Prior Approval Supplement (PAS). • PDUFA V goal date – 4 months	**Type II Variation** • A significant impact on the Quality, Safety or Efficacy of a medicinal product. • Prior Approval Procedure. • Validation + (30, 60, 90)CHMP + 15 days to review and approve.	**Type C** • Require prior approval before implementation. • Should be reflected under "Amendment History" in the MRF1 1Ac) / Module 1.2.1 f) (refer section 2.2 of this guideline)
Moderate Change • A moderate potential to have an adverse effect on the identity, strength, quality, purity, or potency of the drug product. • CBE 30 – Submission at least 30 days before distribution of the post change product. • CBE 0 – Distribution can occur when FDA receives the supplement.	**Type IB Variation** • Minor variation which is neither a Type IA variation nor a Type II variation nor an Extension. • Notification Procedure. • Validation + 30 days.	**Type B** • Require notification. • Should be recorded and made available for inspection. • Should be reflected under "Amendment History" in the MRF 1Ac) / Module 1.2.1 f).
Minor Change • Minimal potential to have an adverse effect on the identity, strength, quality, purity, or potency of the drug product. • Annual Reportable	**Type IA/IA IN Variation** • A minimal impact or no impact at all, on the quality, safety or efficacy of the medicinal product concerned. • Notification Procedure. • 30 days.	**Type A** • Do not require prior approval before implementation. • Do not require prior notification.

COMPARISON OF FDA, EMA AND MCC GUIDANCE ON POST APPROVAL CHANGES

TABLE 2: COMPARISON OF FDA, EMA AND MCC GUIDANCE

FDA[1-2]	EMA[3-6]	MCC[7]
1. Composition Changes:		
Major Changes	**Type II Variation**	**Type C**
Changes are those that are likely to have a significant impact on formulation quality and performance. Tests and filing documentation vary depending on the following three factors: therapeutic range, solubility, and permeability.	Qualitative or quantitative changes in one or more excipients that may have a significant impact on the safety, quality or efficacy of the medicinal product.	Addition or removal or increasing or decreasing any release controlling ingredient.

Moderate Changes Changes are those that could have a significant impact on formulation quality and performance.	**Type IB variation** Replacement of a single excipient with a comparable excipient with the same functional characteristics and at a similar level.	**Type B** Film coating change from organic solution to aqueous solution.
Minor Changes	**Type IA variation**	**Type A**
Changes are those that are unlikely to have any detectable impact on formulation quality and performance.	Any minor adjustment of the quantitative composition of the finished product with respect to excipients.	Deletion of colour/flavour/fragrance.
2. Manufacturing Site Changes:		
Major Changes	**Type II Variation**	**Type C**
A move to a different manufacturing site.	Site which requires an initial or product specific inspection.	Changes in location, involving or affecting environmentally controlled manufacturing or related support areas.
Moderate Changes	**Type IB**	**Type B**
A move to a different manufacturing site for the manufacture or processing of any drug product, in-process material, or drug substance that is not otherwise provided for in this guidance.	Site where any manufacturing operation(s) take place, except batch-release, batch control, primary and secondary packaging, for non- sterile medicinal products.	Changes in responsible individuals specified in approved dossier.
Minor Changes	**Type IA**	**Type A**
A move to a different manufacturing site for secondary packaging	Deletion of manufacturing sites for an active substance, intermediate or finished product, packaging site.	Modification of approved production facility or room(s) that will not have an adverse effect on safety, sterility, purity or potency of product, e.g. adding new interior partitions.
3. Batch Size Changes:		
Major Changes	**Type II Variation**	**Type C**
Changes in batch size beyond a factor of ten times the size of the pilot/biobatch.	The change requires assessment of the comparability of a biological/immunological active substance.	Change in batch size of More than 10-fold compared to the original batch size approved at the time of registration

Moderate Changes	**Type IB**	**Type B**
Change in batch size, up to and including a factor of 10 times the size of the pilot/bio-batch.	More than 10-fold increase compared to the originally approved batch size.	Change in batch size of Up to 10-fold compared to the original batch size approved at the time of registration of the product.
Minor Changes	**Type IA**	**Type A**
Not Mention	Up to 10-fold compared to the originally approved batch size.	Not Mention
4. Manufacturing Process Changes:		
Major Changes	**Type II Variation**	**Type C**
Change in the type of process used in the manufacture of the product, such as a change from wet granulation to direct compression of dry powder.	Substantial change to the manufacturing process of the active substance which may have a significant impact on the quality, safety or efficacy of the medicinal product.	Change in type of process used in the manufacturing of the product outside validation.
Moderate Changes	**Type IB**	**Type B**
Any change in the process, process parameters, and/or equipment except as otherwise provided for in this guidance.	Minor change in the manufacturing process of an aqueous oral suspension.	Change in Equipment or process machinery but with same processing principles.
Minor Changes	**Type IA**	**Type A**
Changes to equipment of the same design and operating principle.	Minor change in the manufacturing process.	Change in process timing and/or operating speeds (if validated), but same final product specifications and content uniformity.
5. Container Closure System Changes:		
Major Changes For liquid and semisolid dosage forms a change to or in polymeric materials of primary packaging components.	**Type II Variation** The change relates to a less protective pack where there are associated changes in storage conditions and/or reduction in shelf life.	**Type C** Changes in composition of the immediate container affecting stability.
Moderate Changes	**Type IB**	**Type B**

A change in the size and/or shape of a container for a nonsterile drug product, except for solid dosage forms without a change from one container closure system to another. **Minor Changes** A change in the number of unit or labeled amount of nonsterile solid dosage form in a multiple-unit container.	Change in immediate packaging of semi-solid and non-sterile liquid pharmaceuticals. **Type IA** Change in shape or dimensions of the container or closure for Non-sterile medicinal products	Changes in composition of the immediate container. **Type A** Update of approved Storage Instructions to align with currently accepted wording and directives.
6. Specifications changes:		
Major Changes Relaxing an acceptance criterion except as otherwise provided for in this guidance. **Moderate Changes** Any change in a regulatory analytical procedure other than those identified as major changes or editorial changes. **Minor Changes** Tightening of acceptance criteria.	**Type II Variation** Deletion of a specification parameter which may have a significant effect on the overall quality of the active substance and/or the finished product. **Type IB** Addition or replacement of a specification parameter with its corresponding test method as a result of a safety or quality issue. **Type IA** Deletion of a non-significant specification parameter.	**Type C** Change of specification limits or modification(s) in potency, sensitivity, specificity, or purity. **Type B** Not Mentioned. **Type A** Tightening of specification limits.
7. Stability changes:		
Major Changes Change in a approved stability protocol. **Moderate Changes** Reduction of an expiration dating period to provide increased assurance of the identity, strength, quality, purity, or potency of the drug product. **Minor Changes**	**Type II Variation** Change in storage conditions of biological/ immunological active substances. **Type IB** Extension of the shelf life of the finished product. **Type IA**	**Type C** A change in storage temperature / conditions of final product. **Type B** Change of storage conditions of an intermediate of an API based on data from stability. **Type A**

Addition of time points to the stability protocol or deletion of time points beyond the approved expiration dating period.	Reduction of the shelf life of the finished product.	Update of approved Storage Instructions to align with currently accepted wording and directives.
8. Labeling Changes:		
Major Changes Changes based on post marketing study results, including, but not limited to, labeling changes associated with new indications and usage. **Moderate Changes** Addition of an adverse event due to information reported to the applicant or Agency. **Minor Changes** Changes in the layout of the package or container label.	**Type II Variation** Change(s) in the Summary of Product Characteristics, Labelling or Package Leaflet due to new quality, preclinical, clinical or pharmacovigilance data. **Type IB** Implementation of change(s) for which no new additional data is required to be submitted by the MAH. **Type IA** Implementation of wording agreed by the competent authority.	**Type C** Labeling changes associated with new indications and usage. **Type B** Addition of a precaution arising out of a post marketing study. **Type A** Editorial changes, such as adding a distributor's name.
9.Administrative Changes:		
Not Mentioned.	**Type II Variation** Not Mentioned. **Type IB** Change in the (invented) name of the medicinal product. **Type IA** Change in the name and/or address of: a manufacturer.	**Type C** Change/additional source of API to a different company where route of synthesis not the same. **Type B** Change/additional source to a different site of the same parent company of API where route of synthesis and specifications are the same. **Type A** Change in the name and/or address of a manufacturer of the API whether or not a European Pharmacopoeia certificate of suitability is available.

RESULTS:

This article will provide a detailed analysis of the current US, European, South Africa regulations and guidance documents for post-approval CMC change management for small molecules based products. It also provide an analysis of the approaches described in FDA draft guidance on Comparability Protocols —Chemistry, Manufacturing, and Controls EMA draft guidance on Post-approval Change Management protocols MCC draft guidance on Post-approval Change Management protocols.

CONCLUSION:

Knowledge of these differences will enable the sponsor of NDA, ANDA to develop the CMC strategy to implement change successfully in US, EU and SOUTH AFRICAregulated markets.

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